REMARKS

Support for the Amendments can be found in the original claims and the Examples. For convenience and completeness, the continuation Sheet of the Office Action is set forth below in italics, with Applicants' remarks interspersed.

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DETAILED ACTION
Continued Examination Under 37 CFR 1.114
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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/25/2005 has been entered.
Status
Claims 1-12 and 14-24 are pending in the application.
All previous rejections under 35 U.S.C. 112, 1st and 2nd paragraphs, are withdrawn in view of Applicant's amendments.
After considering Applicant's arguments, and after reviewing carefully the disclosure Willson/Murphy disclosures, the examiner has concluded the following. Each independent claim under consideration (claims 1 and 10) requires exposing purine bases by a process selected from the group consisting of selective thermal denaturation/renaturation, alkaline denaturation, and restriction enzyme digestion yielding single-stranded overhangs.
With regard to the latter option, Willson/Murphy teach digesting with exo- and endonucleases prior to contacting a sample to and IMAC material (see US 2004/0152076 claims 14-15, paragraph [0114], for example), but does not teach that this produced "exposed" purine bases [and there are possibilities where this would not
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occur, such as cutting with blunt-cutting endonucleases, such that an assertion of inherency could not be made].
Similarly, with regard to "alkaline denaturation", whereas Willson/Murphy apply "alkaline celllysates" to IMAC material (see US 2004/0152076 paragraph [0188], for example), since the actual pH and conditions of the cell lysis are not disclosed, the examiner has reconsidered his earlier assertion that this inherently would produce denatured nucleic acids, thus exposing purine bases. However, there is an embodiment disclosed in the Willson/Murphy references where nucleic acids are subjected to selective thermal denaturation and renaturation.
Based on these considerations, the previous rejections of claims 3, 23 and 24 under 35 U.S.C. 102(a)/(e) over the disclosures of Murphy et al (WO 02/46398) and Willson et al (US 2004/0152076), respectively, are withdrawn since the new basis for rejection is not relevant to these claims. The rejection of claims 1, 2, 4, 6 and 14-17 are maintained, and the rejection is extended to claims 7 and 10.
The rejection of claim 18 under 35 U.S.C. 103(a) over either Murphy et al or Willson et al in view of Hawkins (US 5,898,071) is maintained for the reasons set forth

below.
New grounds of rejection are also set forth below. These will be followed by the previous rejections that have been maintained. Applicant's arguments will be addressed following the rejections.

The Examiner is thanked for withdrawing the above mentioned prior rejections.

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Claim Objections
Claims 6 and 10 are objected to because of the following informalities: these claims use improper Markush form. Each claim recites a limitation "selected from the group comprising", rather than "selected from the group consisting of'. See MPEP 2173.05(h) and Ex parte Dotter, 12 USPQ 382 (Bd. App. 1931). Appropriate correction is required.

The Markush wording has been corrected in Claims 6 and 10.

New Rejections
Claim Rejections - 35 USC § 112
The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claim 10 recites the limitation (emphasis added) "wherein the process for introducing purine base sites is ... " in line 12. There is insufficient antecedent basis for this limitation in the claim. The claim previously recites a process of "exposing purine bases present within either the desired or undesired nucleic acid" (emphasis added), which clearly indicates the purine bases are already present, not "introduced". Furthermore, the claim previously recites that the means of "exposing" is selected from the group consisting of selective thermal denaturation/renaturation, alkaline denaturation and restriction enzyme digestion yielding single-stranded overhangs, whereas the later "wherein" clause recites means for "introducing" which
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include several alternative techniques (use of oligonucleotide dTs, single-stranded DNA binding proteins, minerals, primers, etc).
For purposes of examination over the prior art, the "wherein" clause will be construed as comporting with the rest of the claim (i.e. "introducing purine base sites" will be construed as "exposing purine base sites present").

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
Claim 10 is rejected under 35 U .S.C. 112, first paragraph, as failing to comply with the written description requirement. The c1aim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This is a NEW MATTER rejection. The issues concern the limitation "wherein the process for introducing purine base sites is selected from the group comprising: selective thermal denaturation and renaturation, alkaline denaturation, the use of restriction enzymes yielding single-stranded overhangs, and the use of oligonucleotide dTs, single-stranded DNA binding proteins, minerals, primers, chelated metals or other nucleic acid fragments to facilitate capture and separation of the undesired (or desired) nucleic acid from the desired (or undesired) nucleic acids". This phrase introduces new matter in two ways.

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First, original claim 10 recited most of these alternatives as processes for

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introducing "handles", not purine base sites. While one can appreciate that some of these processes would introduce single-strandedness as a handle, thereby exposing purine base sites, they would not all necessarily introduce purine base sites. For example denaturation would expose purine bases, not introduce them. The disclosure as filed did not describe introducing purine base sites by these methods. This aspect of the rejection might be overcome with respect to certain of the recited alternatives if Applicant can point to support in the original disclosure that clearly describes (explicitly or inherently) how the alternative introduces purine base sites.

Second, the alternative "chelated metals" is not described anywhere in the disclosure as a means to introduce purine base sites or handles. Original claim 10 finds support in paragraph [0026] of the published application:

Processes such as selective thermal denaturation and renaturation, alkaline denaturation, the use of restriction enzymes yielding single-stranded overhangs, the use of oligonucleotide dTs, single-stranded DNA binding proteins, minerals, and the use of primers or other nucleic acid fragments such as complementary DNA are useful for introducing, enhancing, or stabilizing affinity handles (e.g., single strandedness) in the undesired (or desired) nucleic acids to facilitate capture and separation of the undesired (or desired) nucleic acid from the desired (or undesired) nucleic acids, carbohydrate or protein.

Neither this passage nor original claim 10 recites chelated metals as a means to introduce anything (or expose anything, for that matter). Rather, chelated metals are recited as means for capturing and separation.

Claim 10 now mentions "Chelated Metals" as one "process for <u>separation of the desired product from the undesired nucleic acid</u>".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in th is or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7,10 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Reutelingsperger (US 5,296,467) as evidenced by Srivastava (US 5,948,646).

With regard to claim 1, Reutelingsperger taught a process for separating a desired product (poly-A+ RNA; see column 31, line 58) from undesired nucleic acid (the starting material was total RNA, hence the undesired nucleic acid would be that which lacks a poly-A tail, such as degraded RNA, tRNA, rRNA; see column 31, lines 65-66).
The method comprised exposing purine bases present within the desired nucleic acid product (the poly-A tail of RNA consists of purine bases; i.e. adenine (A) is a purine base) by a process of selective thermal denaturation and renaturation (see column 32, lines 1-2: "the solution is heated to 70° C. for 3 minutes and immediately cooled on ice"), followed by capture of the desired nucleic acid product by a technique selective for the exposed purine bases (see column 31, lines 59-60; oligo dT cellulose is selective for binding the poly-A tail of RNA) and separation of the desired product (poly-A+ RNA) from the undesired product (all other RNA) (see column 32, lines 1-19; the various washings of the column would inherently remove the non-poly-A+ RNA, leaving the polyA+ RNA bound to the column; afterwards, the poly-A+ RNA is eluted from the column,thereby separating the desired and undesired nucleic acids.
The thermal denaturation of total RNA exposes the bases of the poly-A tail, as evidenced by Srivastava, who states (column 11, line 50): "Total RNA is denatured to
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expose the poly-A tails. Poly-A+ RNA is then bound to oligo-dT cellulose, with the remainder of the RNA washing through."
With regard to claim 2, the poly-A+ RNA after thermally denaturing would inherently comprise single-stranded nucleic acid in the poly-A+ tail (this is the basis for oligo dT capture; if the poly-A tail were in double stranded form, it would not bind to the oligo dT capture material).
With regard to claim 3, poly-A+ RNA would be sensitive to genomic DNA contamination in a method such as cDNA synthesis (i.e. reverse transcribing RNA into complementary DNA), since the genomic DNA could act as a template in place of the RNA.
With regard to claim 4, the poly-A + RNA after thermally denaturing would inherently comprise single-stranded nucleic acid in the poly-A+ tail (this is the basis for oligo dT capture; if the poly-A tail were in double stranded form, it would not bind to the oligo dT capture material).
With regard to claim 6, Reutelingsperger used poly-dT (i.e. oligo dT cellulose; column 31, lines 59-60).
With regard to claim 7, by thermally denaturing the total RNA preparation, Reutelingsperger introduced single strandedness in the RNA, thereby exposing purine bases.
With regard to claim 10, in light of the discussion under the 35 U.S.C. 112, 2nd paragraph rejection, the claim only differs in reciting additional means for "exposing"
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purine base sites. Therefore, claim 10 is rejected for the same reasoning as discussed for claim 1.

Claims 1and 10 have now been amended to more clearly recite the release of the desired DNA or protein product prior to exposing the purine base handles. This distinguishes from the references because Reutelingsperger's and Srivastava's captured product is mRNA.

With regard to claim 22, Reutelingsperger captured RNA (poly-A+ RNA; see column 32, lines 1-19).

Claim 22 depends on Claim 1 and becomes ipso facto allowable when Claim 1 is allowed.

Claim Rejections - 35 USC § 103
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
Claims 14-17,23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutelingsperger (US 5,296,467) as evidenced by Srivastava (US 5,948,646) in view of Murphy et al (WO 02/46398, prior art of record).
The teachings of Reutelingsperger as evidenced by Srivastava have been discussed. These references did not teach separation by adsorption on chelated metal (claim 14), or more particularly IMAC (claim 16), or the use of magnetic particles (claim 17). These references also did not teach

The Office Action appears to be missing some wording at this point, but the intent is believed to be understood..

With regard to claim 16, Murphy taught a method "for separating poly(A) tailed mRNA from eukaryotic cells comprising the step of passing a solution containing
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eukaryotic cell mRNA through an IMAC column or over an IMAC matrix and separating poly(A) tailed mRNA from other mRNA, where the poly(A) tailed mRNA elutes from the IMAC matrix last because the poly(A) tail has such a high affinity for IMAC matrix, where the poly(A) tails are usually 50-200 bases long" (page 10, paragraph [0046]).
With regard to claim 14, IMAC involves the use of chelated metal ions (page 2, paragraph [0005]).
With regard to claim 15, Murphy taught multi-channel plates ("well plate"; page 12, Table A, Parameter: Support Shape).
With regard to claim 17, Murphy taught (page 21, paragraph [0089]): "The present invention also relates to a magnetic object such as a bead, stirring rod, or the like either coated with an IMAC ligand or where the object has a porous outer surface to which an IMAC ligand has been bonded to, deposited thereon or therein. The present invention also relates to the use of these magnetic objects to batch-wise purify samples containing target single stranded nucleic acid sequences such as RNAs, oligonucleotides, or the like where the single stranded nucleic acid sequences bind to the magnetic object, which can then be removed from the solution, washed free of contaminates and eluted to recover the single stranded nucleic acid sequences."
With regard to claim 23, Murphy taught HIC (hydrophobic interaction chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").
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With regard to claim 24, Murphy taught RPC (reverse phase chromatography; "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Reutelingsperger by substituting the oligo dT cellulose with the IMAC material taught by Murphy. Regarding the obviousness of substituting equivalents known for the same purpose, MPEP 2144.06 states: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." In this

case, Reutelingsperger clearly establishes that oligo dT cellulose was known in the art as a poly~A+ RNA affinity matrix, and Murphy clearly teaches use of IMAC matrix for the same purpose. Furthermore, it would have been obvious to one of ordinary skill to make use of the various forms of supports (magnetic beads, multiwell plates) and secondary chromatography techniques (RPC, HIC), since as demonstrated by the disclosure of Murphy, these were well known in the art of biological purification.

Claim 24 depends on Claim 1 and becomes *ipso facto* allowable when Claim 1 is allowed.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reutelingsperger (US 5,296,467) as evidenced by Srivastava (US 5,948,646) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 14-17, 23 and 24 above, and further in view of Hawkins (US 5,898,071).
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The teachings of Reutelingsperger, Srivastava and Murphy have been
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discussed. These references did not teach processing multiple samples in parallel. Hawkins taught methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel"(column 10, lines 54-60).
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method suggested by the combined teachings of Reutelingsperger, Srivastava and Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantegeous.

Claim 18 depends on Claim 1 and becomes *ipso facto* allowable when Claim 1 is allowed. The combination of these three references appears to have been assembled only by improper hindsight.

Claims 1-4, 6-8, 10, 11, 14-17 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colman et al (Eur. J. Biochem. 91:303-310 (1978)) in view of Murphy et al (WO 02/46398, prior art of record).
With regard to claims 1 and 10, Colman taught a technique for removing contaminating chromosomal (Le. host genomic DNA) from plasmid DNA by selective thermal denaturation and renaturation. See page 307, figure 3, panel B and caption: "The sample was then heated at 100°C for 2 min before rapidly freezing to -70°C ... After thawing to room temperature the sample was immediately subjected to hydroxyapatite chromatography ... Tracks (a) and (b) ColE1 from cleared lysate before and after heat denaturation and chromatography, respectively". See also page 308, column 1, last paragraph:
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We have found that the contaminating chromosomal DNA can be completely removed by heat-denaturing the cleared lysate prior to hydroxyapatite chromatography (Fig. 3B, compare tracks a and b). Unfortunately this procedure does not enable superhelical DNA to be resolved from nicked circles (Fig. 3B, tracks a and b).

See also page 309, column 2, first paragraph:

This contrasting behaviour of the chromosomal and nicked plasmid DNAs might be attributable to the high concentration of complementary plasmid (though not chromosomal) DNA single strands present in the denatured cleared lysate, a situation favouring reassociation.

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The principle of Colman's method therefore was to selectively denature and renature the nucleic acids in the lysate, such that the desired nucleic acid (the plasmid) renatured and was retained on the chromatography material (hydroxyapatite), while the undesired nucleic acid (contaminating chromosomal DNA) remained denatured (i.e. in single-stranded form) and therefore passed through the column, thereby separating the desired and undesired nucleic acids.

While the thermal denaturation/renaturation would have inherently exposed purine bases in the undesired nucleic acid (i.e. the denatured chromosomal DNA), Colman did not teach capture of the desired or undesired nucleic acid by a technique selective for the exposed purine bases.

Murphy taught (page 18):

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[0078] The inventors have found that a compound containing a non-shielded purine or pyrimidine moiety or group such as a single-stranded nucleic acid molecule, *e.g.*, an oligonucleotide or an RNA molecule or a molecule including A, G, C, T or U, have affinity to an IMAC matrix, while a compound that does not contain a non-shielded purine or pyrimidine moiety or group or easily accessible aromatic nitrogen on a purine or pyrimidine moiety or group, such as double-stranded DNA, RNA, RNA/DNA complexes, has little or no affinity to the same IMAC matrix. Thus, the inventors have demonstrated that the affinity of immobilized metals toward nucleic acid bases allows the use of IMAC in the separation of double stranded nucleic acid polymers from single stranded nucleic acid polymers, the purification of plasmid DNA, RNA, and/or the removal of nucleotides and primers from PCR reactions.

Murphy also taught (page 17):

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[0070] The term "non-shielded" means that a purine and/or pyrimidine groups are sufficiently exposed to be able to bind to metal atoms and/or ions immobilized in a matrix, *i.e.*, an IMAC matrix. For example, RNA, co-enzyme A, denatured DNA are all examples of molecules that contain non-shielded purine or pyrimidine moieties or groups. On the other hand, duplex DNA or RNA are examples of shielded molecules containing purine or pyrimidine moieties or groups. Thus, the term non-shielded means a purine or pyrimidine moiety or group sufficiently exposed to be able to bind to a metal and/or ion in an IMAC matrix or ligand.

Murphy also taught (page 46):

[0185] Purification of plasmid DNA is an added advantage of IMAC. Previous work on affinity precipitation of DNA by compaction agents (19) allows for the creation of high purity plasmid preparation without the use of column chromatography. The major contaminant left in the plasmid DNA purified by compaction precipitation is contaminating RNA and linear DNA (1-5%). The IMAC separation technique of this invention is well-suited to bind the remaining RNA (the minor component) and DNA fragments to further purify large quantities of plasmid DNA on relatively small IMAC columns.

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Murphy also taught (page 47, emphasis added):
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Plasmid and RNA Separation

[0189] The nucleic acid discrimination achieved with IMAC suggests application of the method to the purification of plasmid DNA from RNA-rich bacterial lysates. Figure 8 illustrates repeated batch stripping of 1 mL of an alkaline lysate of *E. coli* JM109 containing pBGS19luxwl plasmid with 50 mL of Cu(II)-charged IDA Sepharose per mL of lysate. Control lane 2 shows a lysate after exposure to uncharged IDA Sepharose, showing that the interactions are strictly dependent on the presence of metal ions. Lanes 5-8 trace one supernatant repeatedly exposed to Cu (II) charged IDA Sepharose. The RNA is effectively removed without loss of the closed circular plasmid. The linearized plasmid is also gradually removed, presumably through interactions with damaged, single-stranded regions.

Murphy also taught that one application of his method was "Plasmid DNA with reduced content of nicked and linearized forms" (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Colman by substituting the hydroxyapatite chromatography with IMAC chromatography as taught by Murphy, since Murphy's technique provides a clear advantage over that of Colman. Colman lamented that his technique did not resolve superhelical plasmid from nicked circles (see text cited above), whereas Murphy's method offered the advantage of plasmid DNA with a reduced content of nicked (and linearized) forms. In making this modification, one would have been motivated to retain the selective thermal denaturation/renaturation step taught by Colman, since Murphy taught that denatured DNA contains non-shielded bases subject to separation by IMAC chromatography (see paragraphs [0070] and
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[0078] cited above). Furthermore, it is clear that IMAC is selective for exposed purine bases, based on the data shown in figure 3 and discussed in paragraph [0056], which indicates IMAC has stronger affinity for As and Gs (purines) than Cs and Ts (pyrimidines). Finally, Murphy expressly suggests using IMAC for plasmid purification (paragraph [0185]).

Claims 1 and 10 have now been amended to more clearly recite the release of

the desired DNA or protein product prior to exposing the purine base handles by creating single-stranded regions. This distinguishes from the Murphy and the Colman references. Claims 2-4, 6-8, 11, 14-17 and 21-24 depend on Claim 1 and become *ipso facto* allowable when Claim 1 is allowed.

> *With regard to claims 2, 4 and 7, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently introduce single-strandedness (thereby exposing purine bases) in contaminating RNA and host genomic (Le. chromosomal) DNA.*
> *With regard to claim 3, plasmid preparations are sensitive to host genomic DNA contamination during selective separation (which is why Colman expressed an interest in removing it).*
> *With regard to claims 6, 14 and 16, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently conduct IMAC chromatography, which involves the use of chelated metal (Murphy page 2, paragraph [0005]).*
> *With regard to claim 8, the denaturation/renaturation taught by Colman involved rapidly cooling the sample comprising the contaminating chromosomal DNA to below 65 °C (see caption of figure 3: "rapidly freezing to -70°C").*
> *With regard to claim 11, Colman expresses the sentiment that nicked plasmid is undesirable (page 308, column 1, last paragraph). Murphy taught his method produced*
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> *plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").*
> *With regard to claim 15, Murphy taught multi-channel plates ("well plate"; page 12, Table A, Parameter: Support Shape).*
> *With regard to claim 17, Murphy taught (page 21, paragraph [0089]): "The present invention also relates to a magnetic object such as a bead, stirring rod, or the like either coated with an IMAC ligand or where the object has a porous outer surface to which an IMAC ligand has been bonded to, deposited thereon or therein. The present invention also relates to the use of these magnetic objects to batch-wise purify samples containing target single stranded nucleic acid sequences such as RNAs, oligonucleotides, or the like where the single stranded nucleic acid sequences bind to the magnetic object, which can then be removed from the solution, washed free of contaminates and eluted to recover the single stranded nucleic acid sequences."*

Claims 2, 4 and 7 all depend directly or indirectly on Claim 1 which has now been amended to distinguish Murphy and Colman as discussed above. Claims 2, 4, and 7 become *ipso facto* allowable when Claim 1 is allowed.

> *With regard to claims 21 and 22, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently capture contaminating genomic DNA and RNA.*
> *With regard to claim 23, Murphy taught HIC (hydrophobic interaction chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").*
> *With regard to claim 24, Murphy taught RPC (reverse phase chromatography;*

"Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

Claims 21-24 all depend upon Claim 1 which has now been amended to distinguish Murphy and Colman as discussed above.

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Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Colman et al (Eur. J. Biochem. 91 :303-310 (1978)) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 1-4, 6-8, 10, 11, 14-17 and 21-24 above, and further in view of Hawkins (US 5,898,071).
The teachings of Colman and Murphy have been discussed. These references did not teach processing multiple samples in parallel.
Hawkins taught methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method suggested by the combined teachings of Colman and Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.
Claims 1-4, 6, 7, 9, 10-12, 14-17 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bimboim et al (Nucleic Acids Research 7(6):1513-1523 (1979)) in view of Murphy et al (WO 02/46398, prior art of record).
With regard to claims 1 and 10, Bimboim taught a method for purifying plasmid DNA wherein nucleic acids in a cell lysate are selectively denatured under alkaline conditions (see page 1514, "Principle of the alkaline extraction method"). Such alkaline denaturation (i.e. the separation of the two strands of double-stranded DNA) would
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inherently expose purine (as well as pyrimidine) bases. Bimboim did not teach capturing the desired or undesired nucleic acid product by a technique selective for the exposed purine bases and separation of the desired and undesired nucleic acids.
Bimboim's method resulted in plamid DNA contaminated with a number of undesirable nucleic acids (see paragraph bridging pages 1518-1519 and figure 1, lane e). These included "irreversibly denatured" plasmid DNA, contaminating chromosomal DNA, low molecular weight RNA, and nicked plasmid DNA (i.e. open circular or "OC" DNA).
Murphy taught (page 18):

[0078] The inventors have found that a compound containing a non-shielded purine or pyrimidine moiety or group such as a single-stranded nucleic acid molecule, e.g., an oligonucleotide or an RNA molecule or a molecule including A, G, C, T or U, have affinity to an IMAC matrix; while a compound that does not contain a non-shielded purine or pyrimidine moiety or group or easily accessible aromatic nitrogen on a purine or pyrimidine moiety or group, such as double-stranded DNA, RNA, RNA/DNA complexes, has little or no affinity to the same IMAC matrix. Thus, the inventors have demonstrated that the affinity of immobilized metals toward nucleic acid bases allows the use of IMAC in the separation of double strained nucleic acid polymers from single stranded nucleic acid polymers, the purification of plasmid DNA, RNA, and/or the removal of nucleotides and primers from PCR reactions.

Murphy also taught (page 17):

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[0070] The term "non-shielded" means that a purine and/or pyrimidine groups are sufficiently exposed to be able to bind to metal atoms and/or ions immobilized in a matrix, *i.e.*, an IMAC matrix. For example, RNA, co-enzyme A, denatured DNA are all examples of molecules that contain non-shielded purine or pyrimidine moieties or groups. On the other hand, duplex DNA or RNA are examples of shielded molecules containing purine or pyrimidine moieties or groups. Thus, the term non-shielded means a purine or pyrimidine moiety or group sufficiently exposed to be able to bind to a metal and/or ion in an IMAC matrix or ligand.

Murphy also taught (page 46):

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[0185] Purification of plasmid DNA is an added advantage of IMAC. Previous work on affinity precipitation of DNA by compaction agents (19) allows for the creation of high purity plasmid preparation without the use of column chromatography. The major contaminant left in the plasmid DNA purified by compaction precipitation is contaminating RNA and linear DNA (1-5%). The IMAC separation technique of this invention is well-suited to bind the remaining RNA (the minor component) and DNA fragments to further purify large quantities of plasmid DNA on relatively small IMAC columns.

Murphy also taught (page 47, emphasis added):

Plasmid and RNA Separation

[0189] The nucleic acid discrimination achieved with IMAC suggests application of the method to the purification of plasmid DNA from RNA-rich bacterial lysates. Figure 8 illustrates repeated batch stripping of 1 mL of an alkaline lysate of *E. coli* JM109 containing pBGS19hxwt plasmid with 50 mL of Cu(II)-charged IDA Sepharose per mL of lysate. Control lane 2 shows a lysate after exposure to uncharged IDA Sepharose, showing that the interactions are strictly dependent on the presence of metal ions. Lanes 5-8 trace one supernatant repeatedly exposed to Cu (II) charged IDA Sepharose. The RNA is effectively removed without loss of the closed circular plasmid. The linearized plasmid is also gradually removed, presumably through interactions with damaged, single-stranded regions.

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Murphy also taught that one application of his method was "Plasmid DNA with reduced content of nicked and linearized forms" (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Birnboim by subjecting the alkaline lysate to

IMAC chromatography as taught by Murphy, since Murphy's technique provides a clear advantage over that of Birnboim. Murphy's method offered the advantage of plasmid DNA with a reduced content of nicked (and linearized) forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").
Furthermore, Murphy expressly suggests applying IMAC to alkaline celilysates in order to remove RNA and linearized plasmid (paragraph [0189]). Furthermore, it is clear that IMAC is selective for exposed purine bases, based on the data shown in figure 3 and discussed in paragraph [0056], which indicates IMAC has stronger affinity for As and Gs (purines) than Cs and Ts (pyrimidines).

Birnboim does not teach the use of selective denaturation for changing the conformational state of gDNA to allow selective separation. from plasmid DNA per the Specification para 0011. Combining Birnboim with Murphy still does not read on applicants' three step process of liberation, exposure and capture.

Claims 2, 4 and 7 become *ipso facto* allowable when Claim 1 is allowed.

With regard to claims 2,4 and 7, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently introduce single-strandedness (thereby exposing purine bases) in contaminating RNA and host genomic (i.e. chromosomal) DNA.

Claims 2, 4, and 7 all depend upon Claim 1 which has now been amended to distinguish Murphy and Birnboim as discussed above. Claims 2, 4 and 7 become *ipso facto* allowable when Claim 1 is allowed.

With regard to claim 3, plasmid preparations are sensitive to host genomic DNA contamination during selective separation.
With regard to claims 6, 14 and 16, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would
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Page 22 inherently conduct IMAC chromatography, which involves the use of chelated metal (Murphy page 2, paragraph [0005]).

Claims 6, 14 and 16 all depend directly or indirectly on Claim 1 and become allowable when Claim 1 is allowed.

With regard to claim 9, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently conduct an alkali based process in which genomic DNA or other nucleic acid contaminant was rapidly neutralized and captured by an affinity method (see Birnboim, page 1514, "Principle of the alkaline extraction method").
With regard to claims 11 and 12, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently remove undesired open circular (i.e. nicked) and linear plasmid DNA from supercoiled plasmid DNA. Murphy taught his method produced plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

With regard to claim 15, Murphy taught multi-channel plates ("well plate"; page 12, Table A, Parameter: Support Shape).
With regard to claim 17, Murphy taught (page 21, paragraph [0089]): "The present invention also relates to a magnetic object such as a bead, stirring rod, or the like either coated with an IMAC ligand or where the object has a porous outer surface to which an IMAC ligand has been bonded to, deposited thereon or therein. The present invention also relates to the use of these magnetic objects to batch-wise purify samples containing target single stranded nucleic acid sequences such as RNAs, oligonucleotides, or the like where the single stranded nucleic acid sequences bind to Application/Control Number: 10/737,403 Art Unit: 1637
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the magnetic object, which can then be removed from the solution, washed free of contaminates and eluted to recover the single stranded nucleic acid sequences."
With regard to claim 20, by carrying out the alkaline denaturation step taught by Bimboim, followed by IMAC chromatography taught by Murphy, one would inherently capture linear plasmid DNA. Murphy taught his method produced plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product"); see also paragraph [0189].
With regard to claims 21 and 22, by carrying out the alkaline denaturation step taught by Bimboim, followed by IMAC chromatography taught by Murphy, one would inherently capture contaminating genomic DNA and RNA.
With regard to claim 23, Murphy taught HIC (hydrophobic interaction chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").
With regard to claim 24, Murphy taught RPC (reverse phase chromatography; "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

Claims 9, 11, 12, 17, 20-24 all depend upon Claim 1 which has now been amended to distinguish Murphy and Colman as discussed above.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bimboim et al (Nucleic Acids Research 7(6):1513-1523 (1979)) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 1-4, 6,7,9, 10-12, 14-17 and 20-24 above, and further in view of Hawkins (US 5,898,071).
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The teachings of Birnboim and Murphy have been discussed. These references did not teach processing multiple samples in parallel.
Hawkins taught methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method suggested by the combined teachings of Bimboim and Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.
Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bimboim et al (Nucleic Acids Research 7(6):1513-1523 (1979» in view of Murphy et al (WO02/46398, prior art of record) as applied to claims 1-4, 6, 7, 9, 10-12, 14-17 and 20-24 above, and further in view of Cohen et al (US 5,945,522) and Cherwonogrodzky et al (US 2001/0055780).
The teachings of Birnboim and Murphy have been discussed. In particular, it was explained in the discussion of claim 20 as to how one would have arrived capturing linear plasmid DNA. The Birnboim and Murphy disclosures did not teach or suggest copying BACs, PACs or Y ACs, which are particular species of large plasmids.
Cohen taught purifying BAC DNA by alkaline lysis of cells followed by centrifugation on cesium chloride gradient to obtain purified BAC DNA (column 15, lines

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45-50). Birnboim also discusses cesium chloride centrifugation to separate closed circular plasmid DNA from open circular or linear DNA (page 1513, "Introduction"). Cherwonogrodzky taught that cesium chloride centrifugation was costly and time consuming (paragraph [0061]). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method suggested by the combined teachings of Birnboim and Murphy to purify BAC DNA, which would inherently result in capturing linear BAC DNA on the IMAC material. One would have been motivated to purify BAC DNA since Cohen evidences that purification of BAC DNA was desired in the prior art,and one would have been motivated to use Murphy's IMAC technique instead of Cohen's cesium chloride technique because Cherwonogrodzky taught that the latter approach was costly and time consuming. Murphy taught, on the contrary, that "IMAC worked well as a fast and efficient means of stripping RNA from a plasmid containing lysates" ([sic], page 46, paragraph [0187]). Murphy also taught the IMAC approach removed linear plasmid DNA (paragraph [0189]). Hence, by purifying BAC DNA according to the combined teachings of Birnboim and Murphy, one would have inherently captured linear plasmid (BAC) DNA.

Claims 18 and 19 depend on Claim 1 which now recites more clearly liberating the desired product from any cell within which it is contained; and thereafter exposing the purine handles.

Double Patenting
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference c1aim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference c1aim(s). See, e.g., In re Berg, 140
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Page 26F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046,29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Omum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).
Claims 1-4, 6-12 and 14-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-12, 16, 22-25, 29, 30, 32, 34-36, 38, 40-43 of copending Application No. 09/994,701 in view of Colmanet al (Eur. J. Biochem. 91 :303-310 (1978)). The claims of the '701 application teach separating and purifying nucleic acids having at least 4 non-shielded purine or pyrimidine bases using IMAC chromatography. IMAC is inherently selective for purine bases as shown by figure 3 of the instant application. The claims of the '701do

not teach exposing purine bases by a process of selective thermal denaturation and renaturation. Colman taught using selective thermal denaturation and renaturation to separate and purify nucleic acids.
It would have been obvious to one of skill in the art to use selective thermal denaturation and renaturation to expose purine bases and use IMAC as taught in the instant claims, since one of skill in the art would have understood this was a way in which the bases in nucleic acids could be exposed based on the teachings of Colman
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(note also that claim 34 of the '701 application specifically teaches denatured DNA as an example of nucleic acids with exposed purine and pyrimidine bases). This is a provisional obviousness-type double patenting rejection.

A Terminal Disclaimer re USSN 09/994,701[Attorney Docket 012AUS IMAC] was enclosed with Applicants' 2 April 2009 response and is incorporated by reference herein.

Previous Rejections
Claim Rejections - 35 USC § 102
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless -
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351 (a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21 (2) of such treaty in the English language.
Claims 1,2,4,6,7,10 and 14-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Willson et al (US 2004/0152076) or alternatively under 35 U.S.C. 102(a) as being anticipated by Murphy et al (WO 02/46398). As the disclosures of these references are identical, reference will only be made to teachings in US 2004/0152076.
Willson teaches a method for mismatch detection using IMAC (paragraphs [0229]-[0230]). Specifically, Willson teaches (emphasis added): "Higher resolution IMAC HPLC can separate mismatch-bearing oligonucleotide heteroduplexes, presumably through interactions with bases in the disordered region ... Especially with the enhanced resolution of metal affinity capillary electrophoresis (22), this mismatch separation could serve as the basis of PCR product cleanup, SNP scoring, or
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hybridization assays. Fragmentation of a potentially mutated gene followed by heat denaturation and reannealing in the presence of the correspondinQ wild type DNA, could allow efficient DNA sequence confirmation by IMAC in an analysis similar to "tryptic mapping" of proteins." Reannealing is the same thing as renaturing. If one were to heat denature and reanneal a mixture of mutant and wildtype DNA, one would produce a mixture of three types of duplexes: the mismatched heteroduplex (a mutant strand annealed to a wildtype strand), as well as the two original homoduplexes (mutant/mutant and wildtype/wildtype). Therefore, this embodiment anticipates claim 1 because it comprises: exposing purine bases present within the desired nucleic acid product (Le. the heteroduplex)through a process of selective thermal denaturation and renaturation,

> *followed by capture and separation of the desired product (the heteroduplex) from the undesired nucleic acid (the two residual homoduplexes).*
> *With regard to claims 2, 4 and 7, Willson introduces single-strandedness into the molecules to be captured as discussed for claim 1, Le. the production of a mismatch. Even if the mismatch is only at a single nucleotide, there is no particular length of single-strandedness required by the claims. With regard to claims 6, 14 and 16, Willson teaches IMAC (paragraph [0230]). With regard to claim 14, Willson teaches IMAC (paragraph [0120]), which comprises adsorption on chelated metal (paragraph [0007]).*
> *With regard to claims 15 and 17, Willson teaches that duplexes bearing mismatches can also be analyzed using a microtiter well (which implicitly teaches a Application/Control Number: 10/737,403 Art Unit: 1637 Page 29 microtiter plate, Le. a "multi-channel plate") as well as IMAC beads (see paragraph [0101]). Furthermore, Willson teaches that such beads can be magnetic (page 5, Table A, "Support Shape").*

The rejection of Claims 1,2,4,6,7,10 and 14-17 under 35 U.S.C. 102(e) as being anticipated by Willson et al (US 2004/0152076) or alternatively under 35 U.S.C. 102(a) as being anticipated by Murphy et al (WO 02/46398) must be respectfully traversed. For anticipation under 35 USC 102, every feature of the claims must be taught by the single reference. Independent Claims 1and 10 have now been amended to more clearly recite the release of the desired product prior to exposing the purine base handles. This distinguishes from the Willson and Murphy references because they do not teach the 3-step process of the present claims, as discussed above.

Claims 2,4,6,7 and 14-17 depend on Claim 1 and become *ipso facto* allowable when Claim 1 is allowed.

> *Claim Rejections - 35 USC § 103*
> *The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:*
> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*
> *This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).*

The invention was commonly owned and remains so.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Willson et al (US 2004/0152076) or Murphy et al (WO 02/46398) in view of Hawkins (US 5,898,071). The teachings of Wilson and Murphy have been discussed. Neither of these references teaches processing multiple samples in parallel.
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Hawkins teaches methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method of either Willson or Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.

Claim 18 depends on Claim 1. Claim 1has now been amended to more clearly recite the release of the desired product prior to exposing the purine base handles. This distinguishes from the Murphy and Willson references as discussed above. The combination of these three references appears to have been made only by improper hindsight.

Response to Arguments

Applicant's arguments filed 07/13/2008 have been fully considered but they are not persuasive. Applicant argues (page 11) that "the concept of deliberately and selectively exposing purine bases within the desired (or undesired) molecule to provide handles for its separation is novel and is not disclosed in the Murphy reference." Similar remarks are presented in the first paragraph of page 12. This argument is not persuasive, since it is explained in the revised rejection that in fact Willson/Murphy deliberately denatures and reanneals to form a mismatched heteroduplex. With regard to the terms "desired" and "undesired", the claims do not set forth any requirements as to what constitutes a desired or undesired product. Clearly the intent was to separate the heteroduplex from non-heteroduplex; in this regard, the heteroduplex can be regarded as a "desired" molecule.
Applicant also argues that the feature of "exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid by a process selected from the group consisting of selective thermal denaturation and renaturation, alkaline
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denaturation, and restriction enzyme digestion yielding single-stranded overhangs ... was not obvious to Professor Willson, the lead inventor, a person well skilled in the Art ... at the time the invention claimed in the Murphy (Willson) reference was made." This argument is also not persuasive. As set forth in MPEP 2112(11): "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377,67 USPQ2d 1664, 1668 (Fed. Cir. 2003)". Thus, Applicant's failure to appreciate at the time that the Willson/Murphy disclosure taught the method as claimed is not relevant. The heteroduplex separation embodiment discussed in the revised rejection teaches claimed method.
Conclusion

Claim 5 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The closest prior art is Heisler et al (US 5,843,654), who taught purifying recombinant Taq using IMAC. However, in this case, Heisler captured the Taq on the IMAC material by virtue of the histidine tag artificially incorporated in the Taq protein. One would not have been motivated to combine Heisler with the instant methods, since the instant methods are based on capturing nucleic acids on the IMAC material as well as the histidine-tagged Taq protein. Therefore, separation of Taq from contaminating host DNA would not be achieved.

The Examiner is thanked for indicating the allowability of Claim 5 which has now been rewritten in independent form, also using the phrase "recombinant polymerase" as the recovery of *taq* and all recombinant polymerase is unobvious over the references of record. Dependent Claim 16 now recites the Taq product.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
/Samuel Woolwine/ Examiner, Art Unit 1637
/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637

Claim 10 has been further amended previously to require either thermal denaturation/renaturation, alkaline denaturation or the use of restriction enzymes yielding single-stranded overhangs, to conform to Claim 1 in this respect. Claims 1, 5 and10.

The amendments clarify the claims and point out more clearly what Applicants regard as thir invention. No new matter or estoppel is involved.

The one-month Extension Fee, the Terminal Disclaimer Fee and any other necessary (small entity) charges can be charged to USPTO Deposit Account 200336 of Technology Licensing Co. LLC. Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,

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[Enclosure: Terminal Disclaimer was enclosed with 2 April 2009 Amendment]